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MINI-REVIEW

Non-transplant surgical management of end-stage heart failure

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Summary Despite a variety of available medical therapies and electrophysiological interventions, many heart failure patients still have a poor quality of life and a poor prognosis. Cardiac transplantation is currently the main treatment for end-stage heart failure in Taiwan but it is sometimes accompanied by rejection, immune compromise, and the adverse side effects of antirejection drugs. In addition, there is a shortage of donor grafts worldwide. For these reasons, other surgical interventions that alleviate ischemia and valvular dysfunction, and also reverse ventricular remodeling, should be considered before transplantation is advised. In this review, we discuss current nontransplant surgical management strategies for end-stage heart failure in terms of coronary revascularization, mitral reconstruction, ventricular reconstruction, and stem-cell regeneration of the myocardium.

1. Introduction

Despite significant advances in medical therapy such as the aggressive use of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, the main current treatment modality for congestive heart failure is orthotopic cardiac transplantation. Because donor supply is extremely limited, only 623 heart transplants were performed in Taiwan from 1997 to 2007 according to data from the Bureau of National Health Insurance, Department of Health, Executive Yuan, Taiwan R.O.C. Furthermore, data from the Taiwan Organ Registry And Sharing Center show 84 cases in 2008, 90 in 2009 and 80 in 2010. Nontransplant surgical procedures will undoubtedly play an important role in the future. In this review, we discuss nontransplant surgical therapy for end-stage heart failure. Mechanical circulatory support is a wide topic and has been purposely excluded from this review.

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2. Coronary revascularization

Ischemic cardiomyopathy is caused by occlusive or obstructive coronary artery disease. Ischemic cardiomyopathy is now recognized as the most common cause of heart failure worldwide.[1–4] It can be described in terms of three pathophysiological processes. (1) Myocardial hibernation. This is caused by reduced coronary blood flow that can be partially or completely restored to normal by myocardial revascularization. (2) Myocardial stunning. The viable myocardium is injured by generation of oxygen-derived free radicals on reperfusion and by a loss of sensitivity of contractile filaments to calcium. With adequate revascularization, the postischemic contractile dysfunction of the myocardium can be reversed. (3) Myocardial cell death. This is an irreversible state and causes ventricular remodeling and contractile dysfunction. Myocardial revascularization can save a jeopardized but still viable myocardium, but the aims of surgery should be to elicit a significant improvement in heart failure symptoms, survival rate, and left ventricular (LV) function. Appraised by means of positron emission tomography (PET), nuclear thallium studies, or dobutamine echocardiography tests, the presence of a hibernating or viable myocardium is essential for improvement in the left ventricular ejection fraction (LVEF) after surgical revascularization. Recent studies suggest that at least 25% of the myocardium should be viable for revascularization to be successful.[5,6] In contrast, there is no survival benefit to revascularization for patients with no myocardial viability.[7] Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines for coronary artery bypass graft (CABG) in patients with poor LV function recommend surgery as a Class I indication for patients with left main coronary artery disease or its equivalent as a Class IIa indication for patients with viable noncontracting muscle, and as a Class III indication for those without evidence of ischemia or viability.[8,9]

According to the SHOCK trial (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock), for patients with acute myocardial infarction (MI), the 1-year mortality rate was 42% for CABG, and 56% for medical therapy alone. Furthermore, for patients in cardiogenic shock, the 1-year mortality rate was 56% for CABG and 75% for medical therapy alone.[10] Multiple studies have demonstrated improvements in survival, ventricular function, and functional status after coronary revascularization in patients with ischemic cardiomyopathy (LVEF less than 25%).[11–13] These series show that the survival rate after CABG ranges from 85 to 88% after 1 year, from 75 to 82% after 2 years, from 68 to 80% after 3 years, and from 60 to 80% after 5 years. Operative mortality ranges from 3 to 12%. Revascularized patients have a better quality of life than patients treated with medical therapy alone and have enhanced mobility, peak oxygen consumption, and functional status. After CABG, the incidence of readmission for congestive heart failure (CHF) is low, and many patients are able to return to work.[11–15] According to the CABG Patch trial, perioperative mortality was 1.3% in patients without angina or heart failure. Mortality was 4.8% in patients with no angina and New York Heart Association (NYHA) Class I or II heart failure, and 7.4% in patients with no angina and NYHA Class III or IV heart failure.[16] Elefteriades and Edwards reported improvement in LVEF from 23.3 to 33.2% and improvement in NYHA functional class from 3.1 to 1.4.[12] In Meluzin's prospective study,[17] 133 patients who underwent CABG or percutaneous coronary intervention were randomized into three groups. Group A consisted of 29 patients with a large amount of dysfunctional but viable myocardium, Group B consisted of 60 patients with a small amount of dysfunctional but viable myocardium, and Group C consisted of 44 patients with a dysfunctional and irreversibly damaged myocardium. Group A demonstrated the greatest functional improvement after revascularization, a lower rate of cardiac events during follow-up (two for Group A versus 18 for Group B, $p < 0.05$, and 17 for group C, $p < 0.01$), and better cardiac event-free survival according to Kaplan–Meier survival analysis. Another study showed that revascularization resulted in a 34% increase in exercise capacity (from 5.6 to 7.5 metabolic equivalents).[18]

In summary, for patients with ischemic cardiomyopathy, coronary revascularization should be considered first. Residual cardiac function and the viability of the myocardium should be assessed using PET, dynamic magnetic resonance imaging, nuclear thallium studies, or dobutamine echocardiography tests. If the amount of viable myocardium is acceptable, coronary revascularization should be performed concomitant with mitral or ventricular reconstruction to prevent progressive ischemia and further heart failure.

3. Mitral reconstruction

Mitral regurgitation (MR) is common in patients with heart failure and is associated with a poor prognosis. Progressive LV dilation can result in functional MR secondary to annular dilation, papillary muscle displacement, or chordal tethering. MR is a risk factor for mortality of nonischemic and ischemic causes.[19] Moreover, MR *per se* causes LV overloading and remodeling, which results in a vicious cycle of worsening MR.[19] The traditional "pop-off valve" hypothesis stated that surgical correction with mitral valve replacement would be associated with a high mortality rate. In 1996, Bolling hypothesized that reconstruction of the mitral valve annulus using an undersized ring would correct valvular competency, alleviate ventricular workload, reverse ventricular remodeling, and improve ventricular function.[20] In the past, the high surgical mortality rate associated with mitral valve replacement was because of loss of the subvalvular apparatus rather than loss of the pop-off valve. Maintenance of the integrity of annular and subvalvular continuity during mitral valve surgery is critical for survival. Surgical mortality was 5% in Bolling's study,[20] which included 140 Class III and Class IV patients with an LVEF of less than 25%. The Acorn clinical trial evaluated the safety and efficacy of mitral valve surgery for advanced heart failure patients in about 30 different centers. The operative mortality rate was only 1.6%. The 1-year and 2-year survival rates were 86.5% and 85.2%, respectively.[21,22] In Bolling's study,[20] heart failure patients who underwent mitral valve surgery demonstrated improved LVEF and decreased end-diastolic volume during 3-year and

5-year follow-ups. In the Acorn clinical trial,[21,22] the majority of patients underwent a complete, small annuloplasty repair. Significant decreases in LV end-diastolic volume, LV end-systolic volume, and LV mass were observed 2 years after the procedure, at which time the NYHA class had decreased from 2.8 to 2.2.

Many randomized trials on ischemic cardiomyopathy have shown that a coronary artery bypass with mitral valve repair improves postoperative NYHA functional class and ventricular remodeling and decreases LV end-diastolic volume, pulmonary arterial pressure, and hospitalization for heart failure.[23,24] Other studies reported low operative mortality rates for coronary artery bypass procedures with mitral annuloplasty in patients with advanced heart failure. In addition, the combination of surgical revascularization and mitral valve repair significantly improved the quality of life of patients with coronary artery and ischemic mitral insufficiency.[25,26]

Regarding mitral valve repair in patients with heart failure, the use of nonflexible rings and downsizing rings are worthy of mention.[23,27] In Spoor's study,[27] the MR recurrence rate was 9.5% for the flexible band or ring and only 2.5% for the nonflexible band or ring. The recurrence rates differ because a nonflexible band or ring enables better fixation in the septal lateral dimension and thus prevents annulus dilation. The 2008 guidelines of the ACC/AHA[28] and the 2007 guidelines of the European Society of Cardiology[29] recommend mitral annuloplasty with a downsizing ring for patients with ischemic MR. Most patients with ischemic MR benefit more from annuloplasty with a rigid downsizing ring than from annuloplasty with a nondownsizing ring. The downsizing technique prevents systolic anterior motion in myopathic patients, probably because of widening of the aorto—mitral angle in hearts with increased left ventricular size. The geometric restoration afforded by mitral reconstruction not only effectively corrects MR, but also achieves surgical unloading of the ventricle.

Finally, two kinds of percutaneous mitral valve repair system are currently being evaluated. Introduced via a catheter through the femoral vein and across the atrial septum, the Edwards Milano II mitral clip (Edwards Lifesciences, Irvine, CA, USA) and the Evalve Mitraclip system (Evalve Inc., Menlo Park, CA, USA) create a permanent coaptation between the leading free edges of the anterior and posterior mitral leaflets. The EVEREST II trial[30] demonstrated that the procedure is safe and that it improves clinical outcome to an extent similar to that of conventional surgery, although it was less effective in reducing MR.

The Viacor percutaneous mitral annuloplasty system (Viacor Inc., Wilmington, MA, USA) and the Carillon mitral contour system (Cardiac Dimensions, Kirkland, Washington, DC, USA) both involve a catheter-based approach to mitral annuloplasty via the femoral vein and the coronary sinus.[31,32] With these systems, a permanent nitinol strut is introduced via the femoral vein and the coronary sinus and wrapped around the posterior annulus of the mitral valve, reducing the anteroposterior dimension of the mitral annulus.

In summary, although mitral valve surgery is associated with a higher mortality rate in patients with advanced heart failure than in those without heart failure, it restores LV remodeling, decreases the NYHA functional class, and affords a better quality of life for patients with ischemic or idiopathic cardiomyopathies. In the near future, the percutaneous mitral valve repair system will be a good choice of treatment when conventional surgery is contraindicated.

4. Geometric ventricular reconstruction

Transmural myocardial infarction may result in ventricular dilation and remodeling, increasing LV wall stress and LV dysfunction, which increase myocardial oxygen consumption and neurohormone and cytokine levels, and cause subendocardial hypoperfusion.[33] Moreover, cardiac workload is increased because of the paradoxical systolic motion of the infarcted myocardium, especially when the dyskinetic region becomes aneurysmal. In the early 1980s, Vincent Dor first demonstrated the use of endoventricular circular plasty to maintain a more physiological cavity.[34] Other terms have been used to describe the same or similar procedures, *viz.*, endoventricular circular patch plasty repair, surgical ventricular restoration, left ventricular infarct exclusion surgery, and left ventricular aneurysmectomy reconstruction. In principle, geometric ventricular reconstruction involves isolation of the infarcted areas and subsequent reduction of left ventricular volumes. Studies conducted since the work of Dor have also revealed significant improvement after exclusion of dyskinetic or akinetic infarcted areas.[35—38]

The RESTORE multicenter study described various techniques for LV reconstruction in heart failure patients after myocardial infarction.[35] The overall 30-day mortality rate after surgical ventricular restoration (SVR) was 5.3% (95% of the patients underwent a concomitant CABG and 22% underwent concomitant mitral valve repair). The ejection fraction increased from 29.6% preoperatively to 39.5% postoperatively. The left ventricular end-systolic volume index (LVESVI) decreased from 80.4 ml/m^2 preoperatively to 56.6 ml/m^2 postoperatively. The overall 5-year survival rate was 68.6%, and the 5-year freedom rate from hospital readmission for CHF, 78%. Preoperatively, 67% of patients were NYHA functional Class III or IV and postoperatively, 85% were Class I or II. In the STICH trial, surgical ventricular reconstruction in combination with CABG reduced the end-systolic volume index by 19%, as compared with 6% for CABG alone. Unfortunately, surgical ventricular reconstruction does not appear to improve symptoms or exercise tolerance or to reduce the rate of death or hospitalization for cardiac causes.[39] And in the new results of the STITCH trial, patients assigned to CABG, as compared with those assigned to medical therapy alone, had lower rates of death from cardiovascular causes and of death from any other causes necessitating hospitalization for cardiovascular disorders.[40]

Other studies have shown improvements in ejection fraction, NYHA class, and long-term survival after significant reductions in the left ventricular end-systolic volume index.[41—45] This procedure is performed regularly and the associated hospital mortality rate is less than 8% and the 12-month freedom from readmission for CHF rate is greater than 80%.

With regard to idiopathic end-stage heart failure, Batista proposed the concept of surgical ventricular remodeling to optimize wall tension and improve myocardial oxygen

consumption in dilated ventricles according to the law of Laplace.[46] Since 1996, he has performed partial left ventriculectomy (PLV) in more than 150 cases, predominantly on patients with Chagas' disease or dilated cardiomyopathy. Unfortunately, no meaningful follow-up data or statistical analyses are available from his series. The Cleveland Clinic performed partial left ventriculectomy (PLV) on 62 patients with idiopathic dilated cardiomyopathy. They reported an operative mortality of 3.5% and a 1-year survival rate of 82%. However, 24 short-term treatment failures were noted, including 11 patients who required left ventricular assist device (VAD) support, six patients who were listed for transplantation, and seven patients who died without left VAD support.[47] Of these 62 patients, 59 (95%) also underwent concomitant mitral reconstruction. Because mitral reconstruction alone could have induced rapid and complete ventricular remodeling,[48] it is difficult to isolate the role of PLV *per se* in correction of ventricular remodeling in the Cleveland Clinic study. At present, there is no definitive evidence for a benefit of PLV in patients with idiopathic end-stage heart failure.

To optimize Laplace's law, dynamic cardiomyoplasty (DCMP) is applied to reduce wall stress by wrapping the latissimus dorsi muscle around the heart.[49,50] The latissimus dorsi muscle is stimulated to contract in synchrony with the heart via an electromyostimulator. Because of the absence of data on hemodynamic or survival improvement, the DCMP is available only in Russia, Europe, Asia and the Caribbean at present. The DCMP concept stimulated the development of passive cardiac support devices, including the Acorn Cardiac Support Device (ACSD; Acorn Medical, Minneapolis, MN, USA) and the Myocor Myosplint (Myocor Medical, St Paul, MN, USA).[51–54] The ACSD, which is made of polyester mesh fabric, is placed outside the ventricles in a posteroanterior orientation. Similar to the DCMP, the ACSD was proved to support the dilated ventricles passively, reduce ventricular wall stress, and prevent further dilation by girdling compression.[55] The Myocor Myosplint directly alters cardiac geometry and reduces ventricular wall stress.[56,57] Under the hypothesis of optimization of the law of Laplace, the Myocor Myosplint is placed through the right and left ventricular walls to achieve a 20% reduction in wall stress. The ACSD and Myocor Myosplint have been proven to suppress further ventricular dilation and to improve ejection fraction in investigational clinical studies. In the future, further studies will be needed to show the safety and long-term efficacy of this kind of device.

5. Stem-cell regeneration of myocardium

Stem-cell regeneration of the myocardium, which replaces myocytes lost from the injured cardiac region, is another alternative nontransplant treatment for end-stage heart failure. The myocardium could be regenerated by injecting stem cells into the damaged heart. The ideal cell types include skeletal myoblasts, peripheral blood stem cells, and bone marrow stem cells. The major modes of delivery consist of direct epicardial injection, percutaneous catheter-based endocardial injection, and percutaneous transluminal coronary injection. Possible mechanisms of myocardial regeneration involve transdifferentiation of stem cells into cardiomyocytes,[58–60] cytokine- and growth factor-mediated endogenous stem cell mobilization, improved homing of stem cells to sites of injury, and induction of antiapoptotic pathways.[61,62] The paracrine hypothesis has been emphasized recently.[63] Indeed, the ideal stem cell would secrete a broad variety of cytokines, chemokines and growth factors that are beneficial for cardiac repair, providing cytoprotection of resident myocytes, upregulation of angiogenesis, and modulation of inflammatory process. And these synergistic effects will promote re-entry of cardiomyocyte sell cycle, recruit endogenous stem cells, and induct secondary humoral effects in the host tissue. All the above-mentioned mechanisms may contribute to neomyogenesis, neoangiogenesis, and alteration of ventricular remodeling. Neomyogenesis results in an overall increase in functional myocardial mass, whereas the neoangiogenesis results in increased capillary density, improving myocardial perfusion and recruiting the hibernating myocardium.

In the early 2000s, Menasché et al published a series on autologous skeletal myoblast transplantation concomitant with CABG in patients with severe heart failure.[64,65] He demonstrated improvement in NYHA functional class and left ventricular ejection fraction 11 months after the CABG. Other studies also showed improved myocardial wall thickening within the injection region and overall improvement in LVEF.[66–68] At the same time as Menasché's publications, Hamano reported autologous bone marrow cell transplantation concomitant with CABG in patients with ischemic heart disease.[69] In 2004, Wollert's randomized controlled trial demonstrated the safety and efficacy of bone marrow-derived cell therapy for acute ST-elevation MI.[70] In his BOOST trial (bone marrow transfer to enhance ST-elevation infarct regeneration), 60 patients were randomized to primary percutaneous intervention with or without intracoronary infusion of autologous bone marrow cells. At the 6-month follow-up, the group with cell therapy showed significant improvement in LVEF (from 50% to 56.7%) as compared with the group that did not receive cell therapy (from 51.3% to 52%). Chen's randomized trial also showed improvement in LVEF, myocardial perfusion, and wall motion in acute-MI patients ($n = 69$) who underwent primary percutaneous coronary intervention concomitant with intracoronary infusion of autologous bone marrow-derived mesenchymal stem cells.[71]

In summary, many preclinical and clinical studies demonstrate that stem cell regeneration of the myocardium is an alternative efficacious treatment for both acute and chronic myocardial injury. Although therapeutic timing and specific safety concerns such as ventricular arrhythmia are always debated, preliminary clinical trials show that cell therapy has positive benefits. At present, more clinical trials are needed to clarify several essential details, *viz.*, the ideal cell type, cell dose, delivery method, and treatment protocol. In the future, stem-cell regeneration of the myocardium may become the preferred option in treating end-stage heart failure.

6. Conclusions

In the past two decades, there has been an expansion of knowledge on the mechanisms and pathology of remodeling

in heart failure. In addition to transplantation and the newly developed mechanical circulatory support technique, surgical therapy is also an attractive new trend in management of end-stage heart failure. Together with optimal medical treatment, these techniques offer patients with advanced heart failure a better quality of life and a better prognosis.

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